REMARKS/ARGUMENTS

Claims 1-14, 16, 17 and 20-25 remain pending in this application. Claims 15, 18, 19 and 26-34 have been cancelled without prejudice to presentation of these claims in a subsequent continuation application. Claims 1, 7, 9, 11, 16, 17 and 20 have been amended to correct grammatical and typographic errors and to further prosecution. Support for the amendments to the claims can be found in the specification and claims as filed. No new matter has been added.

Patent examiners carry the responsibility of making sure that the standard of patentability enunciated by the Supreme Court and by the Congress is applied in each and every case. MPEP 8th Ed. Rev. 4, §2141. The framework for the analysis, provided by the Supreme Court in Graham v. John Deere, 383 U.S. 1, 148 USPQ 459 (1966), is based on four factual inquiries, termed the Graham factors:

1. Determining the scope and contents of the prior art;
2. Ascertaining the differences between the prior art and the claims in issue;
3. Resolving the level of ordinary skill in the pertinent art; and
4. Evaluating evidence of secondary considerations.

Obviousness is a legal determination based on the underlying facts produced by inquiry into the Graham factors. The legal concept of *prima facie* obviousness is a procedural tool of examination that allocates who has the burden of going forward with production of evidence in each step of the examination process. The examiner bears the initial burden of factually supporting any prima facie conclusion of obviousness. If the examiner does not produce a *prima facie* case, the applicant is under no obligation to submit evidence of nonobviousness. MPEP 8th Ed. Rev. 4, §2142.

To establish a *prima facie* case of obviousness three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, not in applicant's disclosure. In re

Vaeck, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991).

The Office Action dated March 1, 2005 drew the Applicants attention to a protest filed November 22, 2004, further stating "The following rejections are adopted from the protest." Since the specific combinations of references proposed by the protester as bases for rejections were not employed in the Office Action, it would be more accurate to state that the Office Action adopted the protester's flawed and superficial characterization of the scope and content of the prior art and the differences between the claimed invention as a whole and the prior art. The Applicant respectfully submits that adoption of the protester's characterization of the scope and content of the prior art as well as the failure to resolve the level of ordinary skill in the pertinent art are fatal to the proper application of the Graham factors. The Applicant further submits that a *prima facie* case of obviousness has not been established.

Defects Of the Protest

Ascertaining The Level Of Ordinary Skill Is Necessary To Maintain Objectivity

The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry. Ryko Mfg. Co. v. Nu-Star, Inc., 950 F.2d 714, 718, 21 USPQ2d 1053, 1057 (Fed. Cir. 1991). If the only facts of record pertaining to the level of skill in the art are found within the prior art of record, the court has held that an invention may be held to have been obvious without a specific finding of a particular level of skill ***where the prior art itself reflects an appropriate level.*** MPEP 8th Ed. Rev. 4, §2141, quoting. Chore-Time Equipment, Inc. v. Cumberland Corp., 713 F.2d 774, 218 USPQ 673 (Fed. Cir. 1983), emphasis added. Here the protestor, Mr. Jeffery Light, is not objective, but on the website of the organization that he founded "Patients not Patents" styles himself as "a committed activist" who is an advocate against medical patents. See http://www.patientsnotpatents.org ("Patients Not Patents is committed to ensuring access to healthcare through litigation, advocacy, and education. Patients not Patents challenges the validity of medical patents before the United States Patent and Trademark Office." A paper copy of the Patients not Patents home page is attached as Exhibit A). Here, the non-objective protestor's reliance on medical school textbooks in determining the scope and contents of the prior art in the field of analgesia and the composition and use of local anesthetics as preemptive analgesic agents cannot be accepted by the Examiner, especially since such a characterization of the scope of the prior art implicitly sets

the level of ordinary skill in the art at the level of a medical student.

The present application claims the benefit of U.S. Provisional Application 60/152,718 filed September 7, 1999. The critical date for the discussion of prior art is thus September 7, 1998. The focus for the analysis of obviousness is the prior art "at the time the invention was made." 35 U.S.C. §103(a).

The Applicant respectfully submits that at the time the invention was made the level of ordinary skill in the art in the field of analgesia and the composition and use of local anesthetics as preemptive analgesic agents is higher than that of a medical student, and at least the level of a practicing physician or surgeon or a Ph.D. pharmacologist. Such physicians, surgeons or pharmacologists rely on the primary medical and scientific literature, scholarly review articles and practice updates more than medical school textbooks. See, for example, Achar, S. & Kundu, S., Principles of office anesthesia: part I. Infiltrative anesthesia. *Am Fam Physician.* 2002 Jul 1;66(1):91-4 (*Stating that the studies that have evaluated the clinical advantages of mixing lidocaine and bupivacaine have been inconclusive, and that if anesthesia is required for more than 30 to 60 minutes, lidocaine with epinephrine or bupivacaine with or without epinephrine is recommended.*) This Achar et al. reference and 23 other non-patent references were submitted with a Supplemental Information Disclosure and filed electronically on July 12, 2006. A paper copy of the Supplemental Information Disclosure is attached herewith as Exhibit B for the Examiner's ready reference.

Mischaracterization Of The Scope And Contents Of The Prior Art

The protest cites only one research report, four anesthesia textbooks and the package insert of Naropin (ropivacaine HCl, a local anesthetic that is not part of the claimed invention).

Impermissive Use of Hindsight in Reconstructing Portions of the Invention from Of The Prior Art

The protest cherry-picks the cited prior art to find parts of the claimed invention while ignoring the clear teachings of sections of the same references on mixtures of local anesthetic that are inconvenient. To imbue one of ordinary skill in the art with knowledge of the invention in suit, when no prior art reference or references of record convey or suggest that knowledge, is

to fall victim to the insidious effect of a hindsight syndrome wherein that which only the inventor taught is used against its teacher. *W.L. Gore & Assoc., Inc. v. Garlock, Inc.* , 721 F.2d 1540, 220 USPQ 303, 313 (Fed. Cir. 1983), *cert. denied* , 469 U.S. 851 (1984). The result is that the claims were used as a frame, and individual, naked parts of separate prior art references were employed as a mosaic to recreate a facsimile of the claimed invention. *Ibid* at 312.

The Applicant Provides Additional Evidence of Non-obviousness Herewith

The Applicant submits that since the inquiry into the Graham factors is flawed and incomplete, a *prima facie* case of obviousness has not been established. Nevertheless, the Applicant provides the following additional evidence:

1. The Supplemental Information Disclosure Statement (Exhibit B) listing 24 non-patent references submitted electronically on July 12, 2006. The 24 non-patent references serve to more completely characterize the scope and content of the prior art.

2. The Declaration of Stephen M. Zappala Under 37 C.F.R. §1.132 (Exhibit C) in which the inventor provides further details of a clinical study described in the specification as filed in which an embodiment of the agent of the present claimed invention was used successfully to provide both local anesthesia and preemptive analgesia in patients undergoing penile surgery.

3. A copy of Catterall, W., & Mackie, K. "Local Anesthetics," pp 331-347 in Hardman, J.G., Gilman, A.G., & Limbird, L.E., eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill, New York, 1996 is submitted as Exhibit D.

4. A detailed analysis of difference between the cited references and the claimed invention is provided below.

Claim Rejections

1. Claims 1-8 and 16-34 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman (U) and Cousins. Claims 18, 19, and 26-34 have been cancelled.

Trade-offs often concern what is feasible, not what is, on balance, desirable. Motivation

to combine requires the latter. *Winner Int'l Royalty Corp. v. Wang*, 202 F.3d 1340, 53 USPQ2d 1580 (Fed. Cir. 2000). None of the references cited, alone or in combination, teach the claimed invention as a whole. None of the references teach or suggest the desirability of the claimed invention as a whole, and thus motivation to combine the references is lacking. The rejection under 35 U.S.C. § 103(a) of claims 1-8, 16, 17, 20-25 is unwarranted and should be withdrawn.

The Seow Reference

The Applicant hereby submits factual evidence that the Seow reference does not anticipate, alone or in combination with any of the cited references, the presently claimed invention ***as a whole.***

The Seow (1982) reference describes a prospective double-blind clinical study using single dose lumbar epidural blockade in healthy patients undergoing lower abdominal surgery (Seow, abstract). The study had been prompted by a resurgence of interest in mixtures of local anesthetic agents; earlier animal studies indicated that it might be possible to retain the favorable characteristics of each component of such mixtures, and in vitro studies were in agreement, provided that pH and concentration of the final solution were adjusted appropriately. Seow, page 177, left column. However, the prospective double-blind clinical study provided two important findings: first, that epidural injection of mixtures of lidocaine and bupivacaine resulted in no advantage over either agent alone, and second, maximum blood concentrations associated with the various mixtures of lidocaine and bupivacaine were the same as if the components had been injected individually. Seow, p. 180. While there was little evidence of any advantage of mixing lidocaine with bupivacaine when maximum clinical doses were injected via the needle, and only one ratio 1:1 mixture of 2% lidocaine and 0.5% bupivacaine (i.e., final concentrations of 1% lidocaine and 0.25% bupivacaine), appeared to have some merit, although the gains were small. Seow, p. 182.

In comparison, the present invention comprises a mixture of 1% lidocaine and 0.25% bupivacaine in a ratio less than or equal to 10:1. Note that the final concentrations of lidocaine and bupivacaine are linked, and in a reciprocal fashion. Thus, the 3:1 ratio of Seow has a final concentration of 1.5% lidocaine and 0.125% bupivacaine and the 1:3 ratio of Seow has a final concentration of 0.5% lidocaine and 0.375% bupivacaine. In contrast, the 1:1 ration of the present invention is 0.5% lidocaine and 0.125% bupivacaine. While the ***ratios*** can overlap, the final concentrations of lidocaine and bupivacaine in the pharmacological agent of the claimed

invention cannot overlap those in the mixture disclosed by Seow, as shown in the tables and figure below.

Claim 1
2% Lidocaine + 0.5% Bupivacaine
Final % Concentration

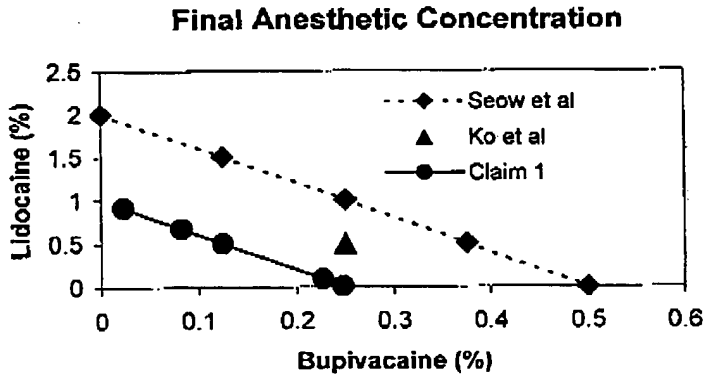
L:B Ratio	Bupivacaine	Lidocaine
10:1	0.023	0.91
2:1	0.083	0.67
1:1	0.125	0.5
0.1:1	0.227	0.091
0.01:1	0.248	0.01

Seow Prior Art Reference
2% Lidocaine + 0.5% Bupivacaine
Final % Concentration

L:B Ratio	Bupivacaine	Lidocaine
No B	0	2
3:1	0.125	1.5
1:1	0.25	1
1:3	0.375	0.5
No L	0.5	0

Ko Prior Art Reference
1% Lidocaine + 0.5% Bupivacaine
Final % Concentration

L:B Ratio	Bupivacaine	Lidocaine
1:1	0.25	0.5



The two lines are parallel and do not meet, demonstrating that even if one of ordinary skill optimizes the pharmacological agent by varying the ratio of the invention of claim 1, the composition disclosed by the Seow reference will not be obtained. Since, the invention of claim 1 must be considered as a whole including all limitations; it is inappropriate and misleading to consider the ratios of the lidocaine and bupivacaine solutions in isolation from other limitations of the claim, the concentrations of the starting the lidocaine and bupivacaine solutions. Seow does not disclose or suggest the invention as a whole of claim 1. Claims 2-8 are dependent on claim 1, and thus incorporate the limitations of claim 1 discussed above. Thus, Seow does not disclose or suggest the invention as a whole of claims 2-8.

Claim 16 as amended includes similar language and limitations to those in claim 1 (" . . . 1% lidocaine HCl solution and 0.25% bupivacaine HCl solution in a ratio less than or equal to 10:1 (volume:volume) . . ") and for the reasons discussed above, Seow does not disclose or suggest the invention as a whole of claim 16.

Claim 17 as amended includes similar language and limitations to those in claim 1 (" . . . 1% lidocaine HCl solution and 0.25% bupivacaine HCl solution in a ratio less than or equal to 10:1 (volume:volume) . . ") and for the reasons discussed above, Seow does not disclose or suggest the invention as a whole of claim 17. Claims 20-25 are dependent on claim 17, and thus incorporate the limitations of claim 17 discussed above. Thus, Seow does not disclose or suggest the invention as a whole of claims 20-25.

<u>Seow In Combination with Goodman & Gilman</u>

The key defect in the Seow reference, that it does not teach or suggest the claimed invention as a whole, discussed above, is not cured by the combination of Seow with Goodman & Gilman.

The Office Action cites Goodman and Gilman, The Pharmacological Basis of Therapeutics, 6th edition, 1980, Macmillan Publishing Co., Inc. Chapter 15, pages 300-320 as a component of the prior art. However, since the inquiry is the scope and content of the prior art as a whole at the time the invention was made, it is appropriate to also consider Chapter 15, "Local Anesthetics" in the then current 9th edition of this standard textbook. A copy of Catterall, W., & Mackie, K. "Local Anesthetics," pp 331-347 in Hardman, J.G., Gilman, A.G., & Limbird, L.E., eds. *Goodman & Gilman's The Pharmacological Basis of Therapeutics*, 9th Edition, McGraw-Hill, New York, 1996 is submitted as Exhibit D. Applicant respectfully submits that one of ordinary skill in the art at the time the invention was made would give more weight to the teachings of the current edition that was only a few years old over the teachings of an edition that was nearly twenty years old.

The Office Action cites Goodman & Gilman as teaching "that in practice, local anesthetics such as lidocaine, which act rapidly but relatively briefly, are often combined with an anesthetic such as bupivacaine, which although slow in onset, has a long duration of action." Page 4 of the Office Action dated 1/13/2006, no page in Goodman & Gilman 6th ed. provided. The same chapter in Goodman & Gilman 9th ed. does not teach that rapid acting local anesthetics are often combined with local anesthetics with slower onset of action, and in fact says nothing

about the topic of mixing local anesthetics at all.

By not pointing out the desirability of the present claimed invention as a whole, Goodman & Gilman fails to provide the motivation to combine its teaching with those of the other cited references. Goodman & Gilman in combination with Seow does not cure the defects of Seow discussed above.

Seow In Combination with Miller

The key defect in the Seow reference, that it does not teach or suggest the claimed invention as a whole, discussed above, is not cured by the combination of Seow with Miller, or combination of Seow with Miller plus Goodman & Gilman.

The Office Action states "Seow does not teach the combination of 1% lidocaine and 0.25% bupivacaine, however, Miller discloses that to create an epidural blockade, the 'usual concentration' range for lidocaine is 1-2% and the 'usual concentration' range for bupivacaine is 0.25% to 0.75% (page 506, table 15-7)." However, the Office Action does not mention that the Miller reference on page 503, column 2, has a section titled "Mixtures of Local Anesthetics." This section discusses only mixtures of chloroprocaine & bupivacaine, and concludes "At present there do not appear to be any clinically significant advantages to the use of mixtures of local anesthetic agents." There is no mention of mixtures of lidocaine & bupivacaine. Applicant submits that by concluding there do not appear to be any clinically significant advantages to the use of mixtures of local anesthetic agents, Miller teaches away from the present claimed invention as a whole. By not pointing out the desirability of the present claimed invention as a whole, Miller fails to provide the motivation to combine its teaching with those of the other cited references. Miller in combination with Seow does not cure the defects of Seow discussed above.

Seow In Combination with Cousins

The key defect in the Seow reference, that it does not teach or suggest the claimed invention as a whole, discussed above, is not cured by the combination of Seow with Cousins, Seow with Cousins and Goodman & Gilman, Seow with Cousins and Miller, or the combination of Seow with Cousins, Miller and Goodman & Gilman.

Cousins teaches away from the presently claimed invention on page 1240 in the section "MIXTURES OF LOCAL AGENTS". "A mixture of an agent with a short duration and rapid onset of action with one that has a slow onset but a long duration has been proposed It is

particularly considered that an amide and an ester should be combined." Cousins further discloses that both lidocaine and bupivacaine are amides, and concludes "Currently, mixtures do not appear to provide significant advantages. The use of continuous technique of administration of the short-acting agents, such as lidocaine or chlorprocaine, provide clinical flexibility." By not pointing out the desirability of the present claimed invention as a whole, Cousins fails to provide the motivation to combine its teaching with those of the other cited references. Cousins in combination with Seow does not cure the defects of Seow discussed above.

2. Claims 9-15 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Seow et al., Miller, Goodman and Gilman (U) and Cousins as applied to claims 1-8 and 16-34, and further in view of Ko et al. This rejection is unwarranted, and should be withdrawn.

As with Seow, while the ratio in which the lidocaine and bupivacaine solutions are combined falls within the ratio range of the claimed invention, the concentration of the bupivacaine solution is different in Ko, and thus the final concentration of the local anesthetics are different. See the tables above and the triangle in the figure above. Again, even if one of ordinary skill were to optimize the pharmacological agent by varying the ratio of the claimed invention, the composition disclosed by the Ko reference will not be obtained. The study of the Ko reference concluded that "compared with healthy control subjects preemptive analgesia did not reduce postoperative pain, reduce analgesic requirements, or shorten the length of hospital stay in patients who underwent an appendectomy." Ko, abstract. This conclusion is in contrast with the finding that use of the agent of the present invention in penile surgery provided the post-operative analgesic benefits of preemptive analgesia. Paragraph 6 of Declaration of Stephen M. Zappala, attached as Exhibit C.

The detailed discussion above of Seow et al., Miller, Goodman and Gilman (U) and Cousins as applied to claims 1-8 and 16-34 above is incorporated by reference. The addition of Ko et al. to the combination does not cure the defects discussed. By not pointing out the desirability of the present claimed invention as a whole, Ko fails to provide the motivation to combine its teaching with those of the other cited references.

Claim 15 has been cancelled. Claim 9 as amended includes similar language and limitations to those in claim 1 (" . . . 1% lidocaine HCl solution and 0.25% bupivacaine HCl solution in a ratio less than or equal to 10:1 (volume:volume). . ") and for the reasons discussed above, Ko alone, or in combination with any or all of the cited references, does not disclose or

suggest the invention as a whole of claim 9. Claims 10-14 are dependent on claim 9, and thus incorporate the limitations of claim 9 as discussed above. Thus, Ko alone, or in combination with any or all of the cited references, does not disclose or suggest the invention as a whole of claims 10-14.

CONCLUSION

In view of the present amendments and remarks, Applicant respectfully submits that claims 1-14, 16, 17 and 20-25 are allowable. Reconsideration, allowance of all claims and early passage to issue are requested. Applicant requests that the Examiner telephone the undersigned if a telephone discussion would be helpful in advancing the prosecution of the present case

Respectfully submitted,
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